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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,789	11/05/2003	Victor J. Dzau	18989-028	7439

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Ingrid A. Beattie, Ph.D., J.D.
Mintz, Levin, Cohn, Ferris,
Glovsky and Popeo, P.C.
One Financial Center
Boston, MA 02111

EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
08/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,789	DZAU ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 91-95* is/are pending in the application.

4a) Of the above claim(s) *4-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12 and 91-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed 6/1/2007 are acknowledged. Claim 1 has been amended, claims 13-19 have been canceled, and claims 91-95 are newly submitted. Claims 4-11 are withdrawn from consideration. Claims 1-3, 12, 91-95 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 6/1/07 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 12 stand rejected under 35 U.S.C. 112, first paragraph, and the rejection now applies to claims 91-95 because the specification, while being enabling for regenerating myocardial tissue by local administration of mesenchymal stem cells expressing an exogenous nucleic acid encoding an akt gene, and a growth factor gene; does not reasonably provide enablement for regenerating myocardial tissue by administering mesenchymal stem cells via any route (claims 94, 95), and it does not reasonably provide enablement for regenerating myocardial tissue with mesenchymal stem cells expressing an exogenous nucleic acid encoding the broadly claimed injury-

associated proteins, or SDF-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for reasons of record.

In the remarks, the applicant argues:

> Applicant teach that certain injury-associated polypeptides e.g. SDF-1 participates in associated polypeptides, e.g., SDF-1 participates in cardiac repair by influencing homing and migration (page 42, lines 7-19, of the specification; Table 3 (page 46 of the specification); and Figs. 19A-B. This discovery, teaching, and indeed forward thinking, by Applicants provide the foundation for the claimed methods that require augmentation of production of SDF-1 by stem cells by introduction of exogenous SDF-1-encoding sequences. Akt-mesenchymal stem cells further comprising SDF-1-encoding nucleic acids provide a reliable, apoptosis-resistant, long-lived stem cell population that localizes to injured tissue – a useful therapeutic tool for tissue regeneration. In fact, subsequent publications (e.g., Zhang et al, 2007, FASEB J., epub May 11, 2007; copy attached as Appendix A) citing Applicant's work confirm that SDF- 1 plays a role in homing of stem cells and progenitor cells to the myocardium as well as trophic support of cardiac myocytes after myocardial infarction leading to enhancement of the regenerative repair process. Thus, not only is adequate guidance provided in the specification as filed to support the full scope of the amended claims, subsequent reports by independent researchers regarding SDF-1 confirms and validates the methods disclosed and claimed. Applicants therefore request withdrawal of this rejection.

In response, it is noted the specification indeed contemplates a method of enhancing migration, homing, or engraftment of a stem cell to an injured tissue by increasing the amount of an injury-associated polypeptide, wherein the said polypeptide is selected from a list of polypeptides including SDF1 (see paragraph bridging pages 8-9), however, the specification only provide evidence that SDF-1, VCAM1, FN1 expression increases upon myocardial infarction (Specification, page 42, table 3 and fig. 19A), it does not provide any evidence that *further increase* of already up-regulated polypeptides such as SDF-1 would enhance stem cell homing. It is also noted that *Zhang et al* cited applicant's work, which reports that mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infracted hearts, SDF-1 was

not mentioned in applicant's publication. In fact, *Zhang et al* teach they were the one first established that SDF-1 expression at a time remote from myocardial infarction can restore stem cell homing to damaged cardiac tissue (see ref. 14 of *Zhang et al, Askari et al,* Lancet 2003;362:697-703). In a commentary to the *Askari* publication, the skilled artisan acknowledges, "SDF-1 MAY HAVE AN IMPORTANT ROLE IN TRIGGERING THESE HOMING EFFECTS. NEVERTHELESS THE MECHANISMS UNDERLYING THE HOMING OF STEM AND PROGENITOR CELLS IN THE TARGET ORGANS ARE POORLY UNDERSTOOD AND DESERVE ATTENTION" (*Franz et al*, Lancet 2003;362:675-6). This illustrated the state of the art and knowledge in the art was such unpredictable, knowing SDF-1 may be beneficial in treating condition of myocardial infarction does not establish the outcome is predictable, it is necessary to conduct further investigation to prove the hypothesis. It appears that *Zhang et al* was the first to provide evidence that supplying nucleic acid encoding SDF1 is beneficial for myocardial repair. As to the genus of injury-associated polypeptides and using such for tissue regeneration, the only support in the specification is prophetic teaching. In view of such, the specification fails to provide an enabling disclosure for what is now claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The previous rejection has been modified in view of the IDS submitted 4/3/07.

Claims 1-3, and 91 are under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *WO 99/03973* (IDS).

Matsui et al teach a method for treating cardiac injury comprising administering an adenoviral vector comprising a nucleic acid encoding a constitutively active Akt mutant via left thoracotomy into the anteroapical myocardium of cardiac ischemia model rats, and reported that Akt activation at the site of cardiac ischemia not only reduced cell death and size of the infarction, but also dramatically improved regional cardiac functions (e.g. the abstract). *Matsui et al* do not teach administering a mesenchymal stem cell genetically modified to express the akt gene.

WO 99/03973 remedy *Matsui et al* by establishing that it was well known in the art that mesenchymal stem cells are capable of differentiating into cardiomyocytes in vitro and in vivo, and thus could be used for regenerating damaged cardiomyocytes (see abstract, and working examples). *WO 99/03973* also teach MSCs could also be genetically modified to enhance myocardial differentiation and integration.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al,* with that of *WO 99/03973*, by administering mesenchymal stem cells expressing an exogenous Akt gene in place of the adenoviral vector as taught by *Matsui et al* with a reasonable

expectation of success. The ordinary skilled artisan would have been motivated to modify the *Matsui et al* process because MSCs have the potential to directly repair and regenerate cardiomyocytes and at the same time deliver the desired transgene. Given that each of the cited references teaches an agent that is effective in cardiac tissue repair/regeneration, one would have had a reasonable expectation of success combining the akt nucleic acid and mesenchymal stem cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant first argue that *Matsui et al* is limited to a nucleic acid therapy, and Greenberger et al teach MSCs as a gene carrier; despite the availability and awareness of host cells that can serve to act as a transgene carrier, almost any cell can act as a transgene carrier, thus there is no reason articulated to combine these two references.

In response, direct administration of a nucleic acid encoding a therapeutic protein or administering said nucleic acid via a host cell were well known alternatives for administering a nucleic acid for gene therapy. *Greenberger et al* do not just teach any host cell, they teach mesenchymal stem cell as a gene carrier, and such teaching was supplemented with *Fukuda et al* who provided motivation to use MSCs in myocardial diseases because they can differentiate to cardiomyocytes, which do not regenerate after birth. Here, MSCs serve two roles, gene carriers and cardiomyocyte replacement.

The amended rejection now relies on *WO 99/03973,* which more clearly teaches that MSCs are capable of regenerating damaged cardiomyocytes *in vivo*, and could carry a transgene promoting the regeneration. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al,* with either *WO 99/03973* or *Greenberger* and *Fukuda et al*, by administering mesenchymal stem cells expressing an exogenous Akt gene in place of the adenoviral vector as taught by *Matsui et al* with a reasonable expectation of success.

Applicant then argues even if the references did establish a prima facie case for obviousness, the specification discloses recombinant Akt-mesenchymal stem cells increased post-transplant survival, i.e. stem cells lacking the akt sequences die with 24 hrs following transplantation, while intramyocardial delivery of akt-MSCs led to a remarkable reduction in infarct volume (44.8% reduction in infarct volume and 84.7% regeneration of lost myocardium). The applicant asserts that this is unexpected result.

In response, it is noted *Matsui et al* teach when administering a nucleic acid encoding akt in the absence of MSCs, it reduced the infarct size by 64% and the number of apoptotic cells by 84%, comparable to or even more efficient than the numbers observed by the applicant. When combined with the effects expected to be brought about by the MSCs, there is a reasonable expectation of success to achieve at least the same if not better therapeutic effect. Thus, the result does not appear to be unexpected. Further, it is noted that the arguments of counsel cannot take the place of

evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). MPEP 716.01(c).

Accordingly for reasons set forth *supra*, the rejection stands.

Claims 12 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *WO 99/03973* as applied to claims 1-3, 91 above, and further in view of *Palasis et al* (US 2002/0172663), for reasons of record and *supra*.

Claims 12, 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *WO 99/03973* as applied to claims 1-3, 91 above, and further in view of *Pillarisetti et al* (Inflammation 2001;25:293), for reasons of record and *supra*.

No claim is allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 4/3/2007 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
July 26, 2007